Risk Assessment in Environmental and
Occupational Health

School of Public Health
Harvard University

Risk of ALAR (daminozide)
Prepared by Susan Moses and Richard Wilson

DATA:

Chemical name DAMINOZIDE (CAS 1596-84-5)

IT is a hydrazine compound that has been used as a plant growth regulator since 1962.

The Environmental Protection Agency (EPA) in 1976 established residue tolerances of 1-55 ppm on variety of fruits that include cherries, plums, apples, nectarines, peaches, pears, grapes, melons, tomatoes, brussel sprouts, peppers and peanuts. Residues of 0.02 - 2ppm are allowed in meat or milk. In 1987 they reaffirmed a limit of 20 ppm on apples.

we selected this as a case study for a number of reasons.

1) It is typical of cases which hit regulators and others out of the blue.

2) Data is sparse and only exists for exposures to animals in rodent bioassays.

3) Immediate action was demanded by a segment of the public.

4) Other hydrazine compounds have been shown to be carcinogenic.

The principal use of ALAR on apples is often regarded as a "non-essential" use, although such phrases depend very much on the individual. Its purpose is to make the apple redder and more attractive: It is also used to control the shelf life of the apple and the market quality at harvest.

ANIMAL BIOASSAY ON DAMINOZIDE:

Daminozide has been treated in a whole life bioassay by the NCI/NTP (National Toxicology Program). It is covered in Technical Report #83 published in 1977.

The reviewers for these data concluded that "under the conditions of these bioassay, daminozide was not carcinogenic in the Fischer 344 rats or in the female B6C3F1 mice. In male B6C3F1 mice, the induction of hepatocellar carcinomas may have been associated with the administration of the test chemical. Daminozide was carcinogenic in female Fischer 344 rats, inducing adenocarcinoma of the endomentrium of the uterus and leiomyosarcomas of the uterus". However, the EPA

decided, on recommendation of their Science Advisory Board, that this was insufficient evidence of carcinogenicity.

Attached (attachment 1) are computer generated plots and significance data from the NCI/NTP data using a program called MSTAGE written by Dr. Crouch.

1. interstitial liver tumors in testis of male rat.
2. lung tumors in female rats.
3. liver tumors in male mice.
4. tumors of uterus in female rats.
5. lung tumors of male mice.

Gold et al in their Carcinogenic Bioassay Data Base (et al includes Bruce Ames) have calculated for Daminozide (Environmental Health Perspectives 58, page 86, 1984).

a "TD50" of	2.15 gms/kg liver tumors ins male mice
	1.24 gms/kg total tumors in male mice
	0.88 gms/kg tumors in male mice
	4.89 gms/kg lung tumors in female rats

This is the dose at which 1/2 the animals could get cancer.

THE METABOLITE UDMH:

In addition we note that there is a metabolite of Daminozide called UDMH. This is produced by Daminozide in the body of the rodents and probably also in people, and may be the active toxic agent, or cancer causing agent (if it causes cancer). Moreover, UDMH is also present, to a few percent, in the apples. (This is the only pesticide where an active metabolite is found in large quantity with the pesticide).

There is no NCI/NTP study on UDMH, but there is a recently concluded study by International Research and Development Co. The results (pp 47 and 48) are attached. There is an increase in lung adenomas at the high dose group as noted on p. 9 of "Summary of Toxicological data on Daminozide and UDMH".

DOSE:

To estimate to people, we need to know exposure.

What was the concentration in apples?
How many apples do people eat?

NRC and EPA in the attached documents make different assumptions.

QUESTIONS

During the next two days the participants should ask the following questions:

1) A simple application of statistical analysis to the data seems to show a statistically significant excess of tumors in animals exposed to DAMINOZIDE. This can be seen in the data as plotted. Gold et al, using a different statistical technique agree.
Why did the EPA reviewers of the NCI document #83 not seem to agree?
What do you think?

2) Is it fair to use the data at the 80ppm dose as evidence for carcinogenicity of UDMH?

3) IF Daminozide and UDMH are assumed to be carcinogenic, what are their potencies ?

4) Which are the reasonable dose scenarios NRDC or EPA or neither?

5) What is the calculated risk on these assumptions?

At the end of the course, Dr. Graham will discuss some management questions with you (refer to attached case).

Attachments

1. Graphs of data from NCI/NTP 83 "DAMINOZIDE"
2. pp. 47 & 48 from IRDC study on UDMH
3. "Intolerable Risk: Pesticides in our children's food: NRDC Feb. 27, 1989.
4. "Daminozide: a special review" EPA, May 1989.
5. Summary of Toxicology data on Daminozide and UDMH (Uniroyal).
6. Letter to Science by Bruce Ames and Lois Gold.